REMARKS/ARGUMENTS

Claims 24-35 and 38-60 are pending in the present application. Claims 29, 30, 33-35, 41, 42, 46, 48, 52, 53 and 55-58 have been withdrawn from consideration. Claims 1-23, 36 and 37 have been previously canceled without prejudice or disclaimer. Claims 24 and 25 have been amended by this Amendment.

Claim Rejections under 35 USC § 102 and 35 USC § 103

Claims 24-28, 31, 32, 38-41, 44, 45, 47, 49-51 and 54 stand rejected under 35 USC § 103(a) as anticipated by Adeyinka et al. (Clin. Cancer Res., vol. 78, pp. 3788-3795, 2002, hereinafter "Adeyinka") in view of Sgroi et al. (Cancer Res., vol. 59, pp. 5656-5661, 1999, hereinafter "Sgroi"). Claims 59 and 60 stand rejected under 35 USC § 103(a) as unpatentable over Adeyinka and Erlander et al. (US 2003/0186248, hereinafter "Erlander"). Applicants respectfully traverse these rejections.

Discussion of Disclosed Embodiments

The following descriptive details are based on the specification. They are provided only for the convenience of the Examiner as part of the discussion presented herein, and are not intended to argue limitations which are unclaimed.

Applicants' disclosed embodiments are directed to reducing an error which is caused by healthy tissue in a sample to be analyzed during clinical diagnostics. At least two sections of a microtome section series of a tissue sample that are not immediately adjacent to each other are stained and evaluated histologically/cytologically, while other sections of the microtome section series that are located between these two sections in the original tissue sample are homogenized

and subjected to non-morphological analytical testing such as, for example, to an array-based mRNA analysis. These sections are selected so that the section or sections sent for non-morphological analytical testing were located between the two sections for histological/cytological evaluation, in situ (in the tissue sample). (See, e.g., paragraph [0054] of published version of the present application (US 2007/0184430)).

As discussed in paragraph 9 of Applicants' published application, the paper "A Gene-Expression Signature as a Predictor of Survival in Breast Cancer" by de Vijver et al. (The New England Journal of Medicine 2002, Vol. 347, 1999) describes a method for analyzing a tissue sample for diseased tissue fractions, in which sections are prepared from the tissue sample, at least one of which is subjected to a histological analysis, while at least one other is subjected to nonmorphological analytical testing, namely, a molecular-biological microarray analysis. In this method, a frozen tissue sample is placed in a microtome, in which a series of sections is prepared. One or more sections of the series are stained with hematoxylin and eosin and histologically evaluated. The fraction of tumor cells in the individual sections is determined. If the fraction is greater than 50%, then corresponding sections from the same series of sections are used for the molecular-biological analysis. If the fraction of tumor cells in the section is less than 50%, then the entire series of sections is discarded. (See paragraph 10 of the published version of the present application). The knowledge about the composition of the sample that is gained from the preliminary histological examination is thus used only to decide whether the sample does or does not satisfy a certain exclusion criterion. (See paragraph 11 of the published version of the present application). The aforementioned method is used in conventional basic research, for example, for developing gene expression data banks, and to do this, it reverts to tissue banks with relatively large numbers of tissue samples. If the sample to be analyzed does not satisfy the

exclusion criterion, a new sample is taken from the tissue bank, histologically reexamined for its fraction of tumor cells, and then, if necessary, subjected to molecular-biological analysis. (See paragraph 12 of the published version of the present application). In clinical diagnostics, on the other hand, where often only a small amount of sample material of an individual patient is available, and a quick analysis result is generally needed -- especially in the case of intraoperative and perioperative diagnostics – the conventional basic research procedure of reverting to the tissue bank is impracticable. Specifically, if it were found during the preliminary histological examination of a patient-specific sample that the fraction of tumor cells is too small, and thus the sample does not satisfy the exclusion criterion, it would be necessary to dispense with the molecular-biological analysis altogether, because the available sample material would already have been used and/or no more time would be available to take and analyze a new sample. In a clinical-diagnostic setting, the method described above for basic research thus would not allow a molecular-biological analysis of all tissue samples in addition to the histological evaluation. (See paragraph 13 of the published version of the present application).

Arguments

Independent claim 1 has been amended to recite: "during clinical diagnostics", "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ."

As stated in MPEP §2143, to reject a claim based on a combination of references, Office personnel must articulate the following:

(1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;

(2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately;

(3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

At least the first, second and third requirements are not met by the Examiner's rejection because (1) Adeyinka and Sgroi are directed only to methods for conventional basic research, and not to methods for use during clinical diagnostics and (2) Sgroi fails to disclose "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ", as expressly recited by independent claim 24.

As stated in MPEP 2143.01, the mere fact that references can be combined or modified does not render the resultant combination obvious unless **>the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007). The mere existence adjacent immunohistochemical staining of tissue sections adjacent to slices used for LCM in Sgroi does not mean that such a process would be obvious to use in the method of Adeyinka, or that even if Adeyinka and Sgroi were to be combined a process resulting from the combination thereof would be obvious to use

during clinical diagnostics. MPEP 2143.01 further states that if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). As will be described in more detail below, the processes of Adeyinka and Sgroi would not and could not be used during clinical diagnostics because Adeyinka and Sgroi are directed only to methods for conventional basic research, and not to methods for use during clinical diagnostics.

Adeyinka is directed only to conventional basic research. Adeyinka discloses that the human DCIS tumor samples are obtained from a tumor bank for the method described therein. (See p. 3789, Materials and Methods, Human Breast Tumor Samples, first paragraph). Adeyinka does not disclose, teach or suggest any method performed during clinical diagnostics. Moreover, Adeyinka's process for basic research requires steps for tissue microdissection, RNA extraction and microarray cDNA membranes. Adeyinka's process is thus completely unconcerned and incompatible with clinical diagnostics.

Sgroi does disclose that all tissue used for his study is obtained from a modified radical mastectomy specimen from a single patient. (See p. 5656, col. 2, Materials and Methods, LCM, first paragraph). However, Sgroi is directed only to conventional basic research, i.e., detailed molecular genetic analysis of patient tissues. (See the Abstract of Sgroi). That is, Sgroi's method of analysis comprises steps for RNA extraction, RNA labeling and Hybridization and Immunoperoxisdase staining and is therefore available only for conventional basic research, and not for more time-sensitive clinical diagnostics. Indeed, Sgroi process is completely unconcerned and incompatible with clinical diagnostics.

Furthermore, one skilled in the art at the time of the present invention would not have combined the teachings of Adeyinka and Sgroi, which relate to only conventional basic research, to achieve the present invention because they are completely unconcerned with a clinical diagnostics situation in which a surgeon takes a tumor sample from a patient during a clinical operation, and a pathologist immediately slices the sample into different sections to give direct, immediate feedback to the surgeon with respect to whether the sample comprises tumor tissue so the surgeon can make a determination as to how to proceed in the clinical operation. Moreover, as noted above, Adeyinka and Sgroi's processes are unsuited for performance during clinical diagnostics because they are not adaptable for the time-sensitive nature and local clinical restrictions of clinical diagnostics. The skilled artisan therefore would not and could not have combined the basic research methods of Adeyinka and Sgroi to be performed during clinical diagnostics. Indeed, a pathologist conventionally takes a number of slices and investigates them histologically, which means that potential information with respect to a molecular signature is not considered during conventional clinical diagnostics even though such information could be extremely helpful for patient specific therapy. In contrast, Applicants' claimed invention does not change standard clinical protocol by performing "during clinical diagnostics" a method wherein "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ".

Adeyinka and Sgroi therefore fail to disclose, teach or suggest "during clinical diagnostics", "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of

the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ", as now expressly recited by Applicants' amended claim 24. Erlander is likewise directed only to conventional basic research and, thus, fails to cure the deficiencies of Adeyinka and Sgroi discussed above with respect to independent claim 1.

Regarding the second reason, the Examiner considers Sgroi to disclose the claimed selection of tissue sections for histological/cytological examination and non-morphological analytical testing. However, Sgroi explicitly discloses that the sections for histological/cytological examination are consecutive tissue samples. (See caption for Figs. 3A and 3B on page 5660 of Sgroi). The advantages of taking sections for non-morphological analytical testing that are between sections used for histological/cytological examination are disclosed at paragraphs 52-55 of the published application, and are not merely design choice. The prior art cited by the Examiner thus fails to disclose, teach or suggest "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ", as expressly recited by independent claim 24.

Independent claim 24 is accordingly deemed to be patentably distinct over the cited art for at least the foregoing reasons.

Independent claim 25 contains features akin to those discussed above with respect to claim 24 and, therefore, claim 25 is likewise deemed to be patentably distinct over the cited art for at least the same reasons as is claim 24. Claims 26-35 and 38-60, which variously depend

from one of claims 24 and 25, are deemed to be patentably distinct over the cited art for at least the same reasons as are claims 24 and 25, as well as on their own merits.

In view of the foregoing, Applicants respectfully request that the rejections under 35 USC § 102 and 35 USC § 103 be withdrawn.

CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all rejections, and allowance of all pending claims is respectfully solicited.

It is believed that no fees or charges are required at this time in connection with the present application. However, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
COHEN PONTANI LIEBERMAN & PAVANE LLP

By /Alfred W. Froebrich/
Alfred W. Froebrich
Reg. No. 38,887
551 Fifth Avenue, Suite 1210
New York, New York 10176
(212) 687-2770

Dated: March 30, 2011